

REMARKS/ARGUMENTS

Claims 1-2 are pending. Citations to the Specification are directed to U.S. Patent Application Publication No. 2006/0128703 (Dodda Mohan Rao).

Favorable reconsideration is respectfully requested in view of the following remarks.

WITHDRAWN REJECTIONS

Applicant gratefully acknowledges the withdrawal of the rejections as noted in the Office Action of May 22, 2008, at page 2.

REJECTION UNDER 35 USC § 102 AND/OR 35 USC § 103

Claims 1 and 2 stand rejected as anticipated or obvious over Barbachyn et al., U.S. Patent No. 5,688,792, example 5. Claims 1 and 2 stand rejected as anticipated or obvious over Meng. Claims 1 and 2 stand rejected as anticipated or obvious over Pearlman et al. Applicant respectfully traverses these rejections. Since the Examiner has considered these rejections together, they will be addressed together, herein.

In the Office Action of November 8, 2007, with regard to the rejections over Barbachyn, Meng, and Pearlman, the Examiner requested that Applicant provide a showing of how the instantly claimed crystalline form is different from the disclosures of Barbachyn, Meng, and Pearlman (see Office Action of November 8, 2008 at pages 5-6).

In the response of February 4, 2008, Applicant provided the IR spectra of the linezolid compounds as disclosed in Barbachyn, Meng, and Pearlman. The Examiner now maintains that IR data is not sufficient to unambiguously show that the cited prior art solid forms are indeed different from the instantly claimed invention. The Examiner cites the reference of Brittain et al. (pg. 229), which allegedly provides for the current state of the art in the identification of

polymorphism:

"...nonequivalent x-ray powder diffraction pattern is observed for each suspected polymorphic variation. All other methodologies must be considered as sources of supporting and ancillary information; they cannot be taken as definitive proof for the existence of polymorphism by themselves alone."

The Examiner also refers to section 5 of the Office Action, which sets forth that claim 1 refers to a crystalline form of linezolid with peaks "at about" the 2θ values provided. The Examiner argues that the claim does not exclude the presence of other peaks in addition to those claimed. The Examiner further argues that the presence of distinct XR data may not be sufficient to establish a difference in the crystalline form, allegedly since it is well known in the art that purity affects spectral/RD data. The Examiner concludes that absent a purity comparison, distinct differences in XRD/spectral data alone cannot conclusively be a result of different polymorphic forms.

While the Examiner cites the reference of Brittain et al. (pg. 229), which allegedly provides for the current state of the art in the identification of polymorphism, these rejections were first made in the Non-Final Office Action of November 8, 2007. In the Reply filed February 4, 2008, Applicant did not amend claims 1-2, and these claims remain in the form they were in for the Non-Final Office Action of November 8, 2007. The Examiner has added the Brittain reference, but has made this Office Action final. This is improper. Applicant has not had an opportunity to respond to the newly cited reference. Therefore, since these limitations had been pending and under consideration previously, it was improper for the Examiner to have made this action Final, especially given that newly cited art was applied. The newly cited art was not necessitated by Applicant's amendment, as these limitations had been previously

considered. MPEP 706.07(d). However, solely in an effort to expedite prosecution, Applicant has filed the instant Request for Continued Examination.

With regard to the anticipation rejection, in Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987) (MPEP 2131), the CAFC set forth that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference". In the instant case, not every element of the claims is present in the Barbachyn, Meng, or Pearlman reference.

If the claims are rejected as being obvious over any one of Barbachyn, Meng, or Pearlman, the claims are patentable over the Barbachyn, Meng, or Pearlman references for the following reasons. The framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966). Obviousness is a question of law based on underlying factual inquiries. The factual inquiries enunciated by the Court are as follows: (A) Determining the scope and content of the prior art; and (B) Ascertaining the differences between the claimed invention and the prior art; and (C) Resolving the level of ordinary skill in the pertinent art. To establish prima facie obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385 (CCPA 1970). MPEP 2143.03. It is important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. (KSR v Teleflex, 12 S.Ct. 1727, 1740 (US 2007)).

Here, claim 1 is directed to a crystalline linezolid form III, characterized by an x-ray

powder diffraction spectrum having peaks expressed as 2θ at about 7.6, 9.6, 13.6, 14.9, 18.2, 18.9, 21.2, 22.3, 25.6, 26.9, 27.9 and 29.9 degrees. The Examiner argues that the prior art form is encompassed by the instant claims, and that the presence of distinct XR data may not be sufficient to establish a difference in the crystalline form, allegedly because it is well known in the art that purity affects spectral/RD data.

However, the art teaches that XRPD is reliable for determination of distinct polymorphic forms. The Bernstein reference teaches (Bernstein at page 117):

In the case of polymorphic mixtures, or the determination of polymorphic purity, the choice of analytical method is considerably more restricted, and X-ray diffraction is one of the most definitive techniques.

Additionally, the Davidovich reference teaches (Davidovich at page 12):

Powder X-ray diffraction is one of the most useful and widely used analytical methods to determine polymorphs and quantify the forms present in a mixture. Detection limit determination becomes critical in the analysis of mixtures. The sensitivity to detect small amounts of a given phase relative to another is critical in the characterization of polymorphs especially for patent infringement cases.

Furthermore, the US Pharmacopia teaches (US Pharmacopia at page 1843):

The powder methods provide an advantage over other means of analysis in that they are usually nondestructive in nature (specimen preparation is usually limited to grinding to ensure a randomly oriented sample, and deleterious effects of X-rays on solid pharmaceutical compounds are not commonly encountered). The principal use of single crystal diffraction data is for the determination of molecular weights and analysis of crystal structures at the atomic level. However, diffraction established for a single crystal can be used to support specific powder pattern as being, truly representative of a single phase.

Accordingly, the art teaches that XRPD data is reliable to differentiate between different polymorphic crystalline forms. In addition, the Brittain reference, cited by the Examiner, teaches

that methodologies other than XRPD data must be considered as sources of supporting and ancillary information. Applicant has provided XRPD data and IR spectra for the claimed polymorphic forms, and demonstrated that IR data show the polymorphic forms as taught in the Barbachyn, Meng, and Pearlman references are distinct from the claimed polymorphic form III linezolid.

With regard to the Examiner's contention that IR data is not reliable, the Examiner's attention is directed to U.S. Patent No. 6,750,341 (Krochmal et al.) which discloses (column 2, lines 6-7):

Polymorphic forms of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as, infrared spectrometry.

Accordingly, the art teaches that IR data is reliable to differentiate between crystalline polymorphic forms.

With regard to the Examiner's contention that the prior art forms are encompassed by the instant claims, the claims have been shown to be directed to a novel polymorphic form of linezolid. If the Examiner is arguing that the references inherently disclose the crystalline form of linezolid as instantly claimed, then the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. In re Rijckaert, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). "To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is

not sufficient.' " In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999). Here, the Examiner has not met that burden by arguing that Applicant needs to show IR data. "In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

Here, Applicant has provided XRPD data and IR spectra for the claimed polymorphic form, and demonstrated that XRPD and IR data show the polymorphic forms as taught in the Barbachyn, Meng, and Pearlman references are distinct from the claimed polymorphic form III linezolid.

In addition, the art recognizes that the use of different methods for crystallization will produce different crystalline forms of a product. For example, U.S. Patent Application Publication No. 2004/0102523 (Broquaire et al.) is directed to a process for obtaining crystalline forms of the enantiomers of modafinil, and the crystalline forms which it is possible to obtain according to this process. The '523 publication discloses that "[i]n this method, the nature of the solvent selected and the conditions of crystallization selected can be used to direct the preparation of any of the polymorphic forms. Crystallization solvents and conditions will be disclosed hereinafter for each modafinil form, respectively I, III, IV and VII obtained according to this method" ¶[0109]. In the instant case, the Barbachyn reference discloses a method of production of linezolid by heating in ethyl acetate and methylene chloride as solvents (see U.S. Patent No. 5,688,792, Example 5 at column 13 to 14). The Pearlman reference discloses a method of production of linezolid by heating in ethyl acetate as solvent (see WO 9924393

Example 8 at page 19). The Meng reference discloses a method of production of linezolid using acetic anhydride as solvent (see Figure 1). In contrast, the instant application discloses that form III linezolid is produced by heating linezolid in a solvent, such as toluene or xylene (see Specification at ¶[0011]).

Therefore, the assumption that crystallization of linezolid according to the methods as disclosed in Barbachyn, Meng, and Pearlman will yield the same polymorphic form as crystallization according to the method as set forth in the instant application has no basis in fact. Thus, the claimed crystalline form III linezolid is not disclosed or suggested in any of the Barbachyn, Meng, or Pearlman references.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-2 under 35 USC 102(b) and/or 35 USC 103(a) is respectfully requested.

REJECTION UNDER 35 USC § 102 AND/OR 35 USC § 103

Claims 1 and 2 stand rejected as being anticipated or obvious over Perrault et al. Applicant respectfully traverses this rejection.

In the Office Action of November 8, 2007, the Examiner argued that Perrault et al. teaches a solid form of linezolid which is obtained from ethyl acetate. The Examiner admitted that the reference does not teach a specific crystalline form of linezolid, because the inherent feature that defines such form (e.g. XRPD data, IR data, etc.) is not disclosed, and admitted that the difference between the prior art solid and the instantly claimed crystalline form lies on characteristics for which the reference happens to be silent. In order to overcome this rejection, the Examiner requested that Applicant provide a showing of how the instantly claimed crystalline form is different from the disclosure of Perrault (see Office Action of November 8,

2008 at pages 6-7).

In the response of February 4, 2008, Applicant provided the XRPD data of the linezolid form II compounds as disclosed in Perrault et al. However, in the Office Action of May 22, 2008, the Examiner argued that the prior art form as identified by the XR pattern is encompassed by the instant claims, and further argued that the presence of distinct XR data may not be sufficient to establish a difference in the crystalline form, allegedly since it is well known in the art that purity affects spectral/RD data.

However, as set forth above, the Bernstein reference teaches that in the case of polymorphic mixtures, or the determination of polymorphic purity, the choice of analytical method is considerably more restricted, and X-ray diffraction is one of the most definitive techniques, the Davidovich reference teaches that powder X-ray diffraction is one of the most useful and widely used analytical methods to determine polymorphs and quantify the forms present in a mixture, US Pharmacopia teaches that diffraction established for a single crystal can be used to support specific powder pattern as being, truly representative of a single phase. Therefore, the art teaches that XRPD data is reliable to differentiate between polymorphic forms.

In addition, as set forth above, U.S. Patent No. 6,750,341 discloses that polymorphic forms of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy and by other methods such as infrared spectrometry. Therefore, the art teaches that IR data is reliable to differentiate between polymorphic forms. Here, Applicant has provided XRPD data and IR spectra for the claimed polymorphic form, and demonstrated that XRPD and IR data show the polymorphic form as taught in the Perrault reference is distinct from the claimed polymorphic form III linezolid.

As additionally shown above, the art recognizes that the use of different methods for crystallization will produce different crystalline forms of a product, as shown in U.S. Patent Application Publication No. 2004/0102523 (Broquaire et al.). The Perrault reference discloses a method of production of linezolid by cooling in either dimethylformamide or tetrahydrofuran as solvents (see WO 02085849 at page 14). In contrast, the instant application discloses that form III linezolid is produced by heating linezolid in a solvent, such as toluene or xylene (see Specification at ¶[0011]).

Therefore, the assumption that crystallization of linezolid according to the methods as disclosed in the Perrault reference will yield the same polymorphic form as crystallization according to the method as set forth in the instant application has no basis in fact. Thus, the claimed crystalline form III linezolid is not disclosed or suggested in the Perrault reference.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-2 under 35 USC 102(b) and/or 35 USC 103(a) is respectfully requested.

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For at least the reasons set forth above, it is respectfully submitted that the above-identified application is in condition for allowance. Favorable reconsideration and prompt allowance of the claims are respectfully requested.

Application No. 10/524,478
Amendment Dated 8/20/2008
Reply to Office Action of 05/22/2008

Should the Examiner believe that anything further is desirable in order to place the application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned attorney at the telephone number listed below.

Respectfully submitted,

CAESAR, RIVISE, BERNSTEIN,
COHEN & POKOTILOW, LTD.

August 20, 2008

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